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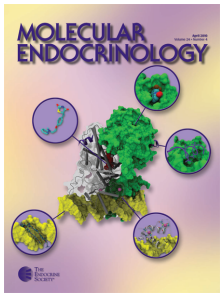

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Auxology Is a Valuable Instrument for the Clinical Diagnosis of *SHOX* Haploinsufficiency in School-Age Children with Unexplained Short Stature

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SHOX **(short stature homeobox-containing gene) mutations causing haploinsufficiency have been reported in some individuals with idiopathic short stature and in many patients with Leri-Weill-dyschondrosteosis. Around 80% of *SHOX* mutations are complete gene deletions, whereas diverse point mutations account for the rest. The aim of this study was to estimate the prevalence of SHOX mutations in children with idiopathic short stature and to give an unbiased characterization of the haploinsufficiency phenotype of such children. We recruited 140 children (61 girls), in our clinic, with idiopathic short stature, which was defined by the presence of normal IGF-I and free T_4; a normal karyotype in females; the absence of endomysium antibodies, of chronic organic, psychological, or syndromatic disease; and by the lack of clear signs of any osteodysplasia. Height, arm span, and sitting height were recorded, and subischial leg length was calculated. Two highly polymorphic microsatellite markers located around the *SHOX* coding region (CA-*SHOX* repeat and DXYS233) were PCR-amplified with fluorescent primers and separated in an automatic sequencing machine. Analysis of parental DNA was performed in the probands who had only one fragment size of each of both markers. *SHOX* haploinsufficiency caused by a *SHOX* deletion was confirmed in three probands (2%), all females, who carried a *de novo* deletion through loss of the paternal allele. Their auxological data revealed a significant shortening of arms and legs in the presence of a low-normal sitting height, when compared with the other 137 children tested. Therefore, the extremities-trunk ratio (sum of leg length and arm span, divided by sitting height) for total height was significantly lower in the three *SHOX* haploinsufficient probands, in comparison with the whole group. This observation was confirmed with the auxological data of five additional patients (four females) previously diagnosed with *SHOX* haploinsufficiency; all but the youngest girl had height-adjusted extremities-trunk ratios more than 1 SD below the mean. All children with SHOX haploinsufficiency exhibited at least one characteristic radiological sign of Leri-Weill-dyschondrosteosis in their left-hand radiography, namely triangularization of the distal radial epiphysis, pyramidalization of the distal carpal row, or lucency of the distal ulnar border of the radius. Our observations suggest that it is rational to limit *SHOX* mutation screening to children with an extremities-trunk ratio less than 1.95 + 1/2 height (m) and to add a critical judgment of the hand radiography. (*J Clin Endocrinol Metab* 88: 4891–4896, 2003)**

HETEROZYGOTE MUTATIONS OF the pseudoautosomal *SHOX* (short stature homeobox-containing gene) causing haploinsufficiency have been reported in some individuals with idiopathic short stature (1, 2) and in many patients with Leri-Weill-dyschondrosteosis (LWD) (3–6), an osteochondrodysplasia with mesomelic short stature and Madelung deformity of the wrist (7). *SHOX* is preferentially expressed in osteoblasts starting in the human embryo from the second month of gestation (8). Alternative splicing generates two proteins, of which the nontruncated SHOXa was shown to induce gene transcription *in vitro* (9). Its exact role in the regulation of bone ontogeny, bone metabolism, and growth is unknown (10). Around 80% of *SHOX* mutations are complete gene deletions, whereas diverse point mutations account for the rest (11). Apart from disproportionate short stature, frequent signs in patients with LWD are cubitus valgus, high-arched palate, and scoliosis, which resemble a segment of the phenotype of females with Turner syndrome who have a *SHOX* deletion on the basis of the X-chromosomal aberration (11, 12). The phenotype of *SHOX* haploinsufficiency is highly variable, even in the same family, indicating a poor genotype-phenotype correlation (5, 11). The initial discovery of a *SHOX* mutation in a child with idiopathic short stature (1) has prompted two questions: 1) How many children with so-far-unexplained (idiopathic) short stature have *SHOX* haploinsufficiency? 2) Is the phenotype recognizable on clinical grounds? Rappold *et al.* (2) reported recently a high prevalence of *SHOX* defects in children with idiopathic short stature, but individuals with parents having Madelung deformity were not excluded from this study, and exact data on auxology and radiology were missing. In contrast, two other groups did not find any *SHOX* defect in children with idiopathic short stature, but in several probands with short stature and signs of LWD (13, 14).

Here, we report the results of a screening for *SHOX* deletion performed in 140 well-characterized children with idiopathic short stature. On this basis, we propose an auxological judgment of school-age children with idiopathic short stature, for narrowing the group of candidates for the molecular analysis of *SHOX*, to those individuals who have a disproportionate growth of their skeleton. In addition, the value of specific radiological signs is discussed.

Abbreviation: LWD, Leri-Weill-dyschondrosteosis.

Subjects and Methods

Individuals

For *SHOX* deletion screening, 140 children (61 girls) with idiopathic short stature [height below the third percentile according to Gerver and

De Bruin (see Ref. 16)] were recruited in our growth research center by three experienced pediatric endocrinologists. The age range was between 2.6 and 16.1 yr (median, 9.1). Idiopathic short stature was defined by the presence of normal IGF-I and free T_4, a normal karyotype in females, the absence of endomysium antibodies, of chronic organic, psychological, or syndromatic disease, and by the lack of clear signs of any osteodysplasia (including Madelung deformity). These criteria were chosen according to the proposed consensus on the definition of idiopathic short stature (15). Height, arm span, and sitting height were recorded in all probands, and subischial leg length was calculated. The probands with a confirmed *SHOX* deletion were re-examined in our clinic, and their routine left-hand radiographs revisited. Left-hand radiographs of the 10 probands with the shortest extremities and no *SHOX* deletion were reanalyzed as well. In addition, auxology and radiology of all children of our clinic with previously detected *SHOX* haploinsufficiency (n = 5) were retrospectively analyzed.

All SD scores are based on the Dutch reference values reported by Gerver and De Bruin (16). Informed consent was obtained from all children and/or their parents.

Methods

Genomic DNA was extracted from blood lymphocytes. Two highly polymorphic microsatellites located on Xp22.3 around the *SHOX* locus were PCR-amplified with fluorescent primers and separated in an automatic sequencing machine as described previously (13); the CA-*SHOX* repeat is located directly distal to *SHOX*, and the DXYS233 around 300–350 kb proximal to *SHOX* (17). Analysis of parental DNA was performed if only one fragment size of each of both telomeric markers (DXYS233, CA-*SHOX* repeat) was present. This analysis enabled us to differentiate between homozygosity (two alleles with identical size) and hemizygosity (loss of one allele).

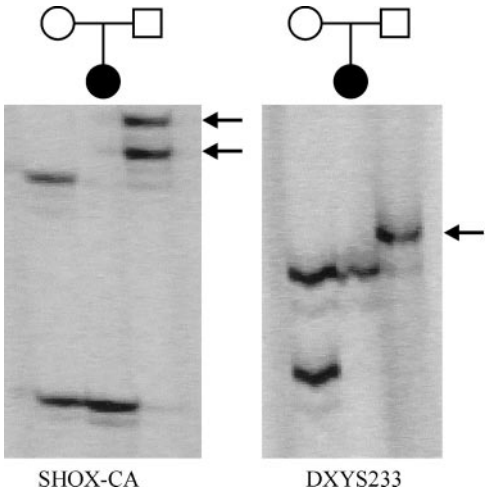

FIG. 1. Electrophoretic analyses of *SHOX*-CA repeat and DXYS233 located distal and proximal to the *SHOX* locus in patient 2. The paternal allele of both markers (*arrows*) is missing, indicating a *de novo* deletion.

Statistical analysis

On the basis of a normal distribution of all auxological parameters measured, differences were considered statistically significant when the respective values of the three children with *SHOX* deletion were outside the 95% confidence interval of the group of children without *SHOX* deletion. All calculations including the fitting of points with lines were computed by JMP Version 4.0.5 (SAS Institute Inc., Cary, NC).

Results

Amplification of two microsatellite markers located at the *SHOX* locus resulted in only one single fragment size at both markers in 11 probands (7%), suggesting hemi- or homozygosity of the *SHOX* locus. For further analysis, parental DNA was available in eight of these 11 probands but was uninformative in two. By amplification of the parental alleles, hemizygosity indicating *SHOX* deletion was confirmed in three girls (2%), who all carried a *de novo* deletion through loss of the paternal allele (Fig. 1). Paternity was proven by amplification of three autosomal markers reported previously (18). A *SHOX* deletion was not excluded in the five probands whose parental DNA was uninformative or missing.

The auxology of the three affected probands was characterized by a short subischial leg length and a short arm span but a low-normal sitting height *for age*. To further investigate this finding, we compared the data with the auxology of the other 137 probands, which were found to be negative for a *SHOX* deletion (Table 1 and Fig. 2, A–C). Whereas target height and weight of the three affected probands were in the 95% confidence interval of the nonaffected group when transferred into SD scores for age, the skeletal proportions of the girls with *SHOX* deletion were significantly different from the probands without *SHOX* deletion, confirming the skeletal disproportion as a specific finding (Table 1). This finding was also evident when arm span, leg length, and sitting height were plotted against height (Fig. 2, A–C).

For the integration of those auxological data that were relevant for the observed skeletal disproportion into one term, we defined an auxological ratio that compares the extremities with the trunk in terms of length (in the following, called extremities-trunk ratio). The extremities-trunk ra-

TABLE 1. Characteristics of the three probands with SHOX deletion, in comparison with the 137 probands tested negative (median, 95% confidence interval)

	SHOX deletion			No SHOX deletion (n = 137) Median (95% interval)
	Patient 1	Patient 2	Patient 3	
Age (yr)	7.3	11.1	13.2	9.1 (4.2 to 14.6)
Target height	−0.10	−2.48	−0.57	−2.14 (−3.69 to −0.19)
Weight	−1.68	−1.31	−1.59	−2.04 (−3.66 to +0.61)
Height	−3.56	−2.69	−2.66	−2.99 (−4.90 to −1.98)
Sitting height/height	+3.82[a]	+3.67[a]	+4.43[a]	+0.41 (−1.33 to +3.29)
Leg length/sit height	−3.28[a]	−3.03[a]	−3.43[a]	−0.52 (−2.87 to +1.56)
Arm span	−3.12[b]	−3.31[b]	−3.42[b]	−2.62 (−5.10 to −1.13)

Data are given in SD scores for age according to Gerver and De Bruin (16).

[a] Values are significant = outside the 95% confidence interval of the group of children without SHOX deletion.

[b] This SD score is no ratio and can therefore not reflect the relative shortening of the arms in comparison with the trunk; the values are outside the 50% confidence interval.

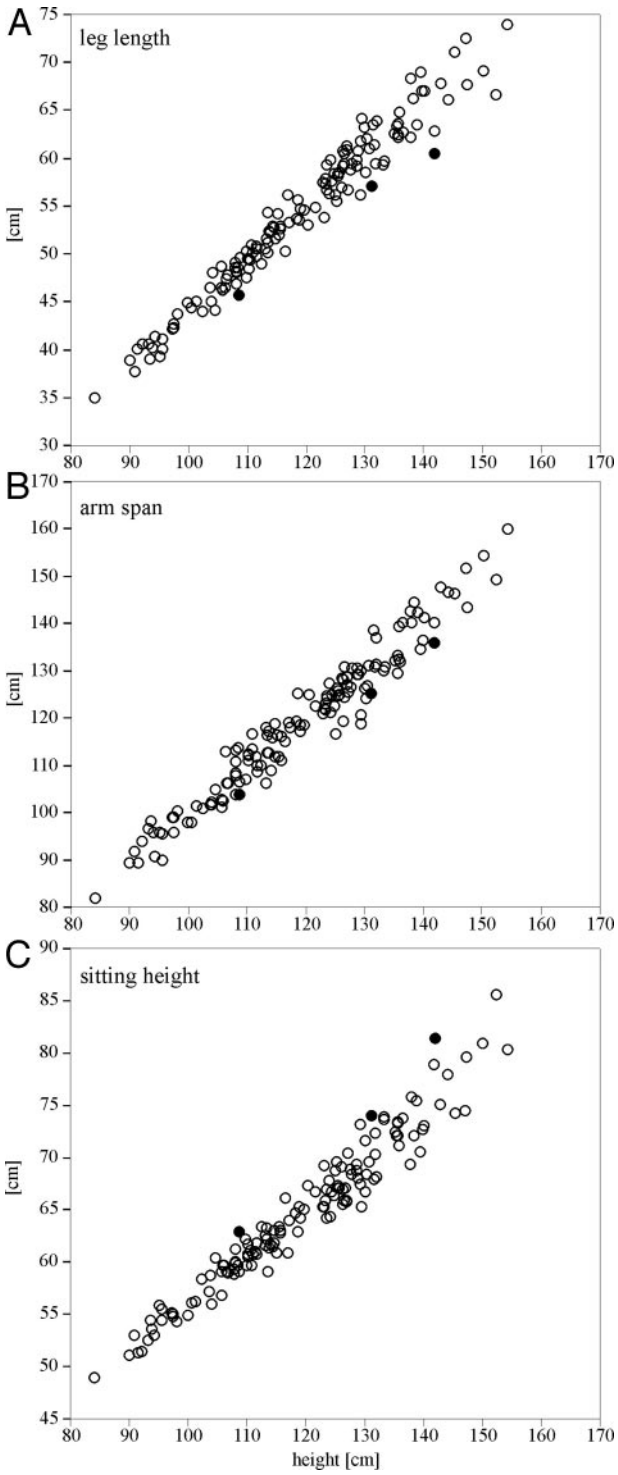

FIG. 2. Subischial leg length (A), arm span (B), and sitting height (C) for height of each proband studied. The *filled circles* mark the three probands with SHOX deletion who have a low leg length and arm span but a high sitting height.

tio was defined as: (calculated subischial leg length + arm span)/sitting height. Therefore, a high extremities-trunk ratio in a short child indicates a disproportionately short trunk, whereas a low extremities-trunk ratio indicates disproportionately short extremities. The extremities-trunk ratios for height of all probands studied are shown in Fig. 3. The graph underlines the observation that the skeletal disproportion of the three probands with *SHOX* deletion (*filled circles*) was a highly specific finding within the total group of screened children with idiopathic short stature. The general linear increase of the extremities-trunk ratio with age and height reflects the physiologically higher velocity of arm and leg growth, in comparison with trunk growth in childhood.

Our data therefore suggested that screening for *SHOX* mutations is only rational in a subset of children with idiopathic short stature, namely in those with disproportionate short stature whose auxology accounts for a low extremities-trunk ratio. Such an auxological criterion would exclude approximately 84% of short-statured children from genetic screening if the upper screening limit is defined as an extremities-trunk ratio of one SD below the height-adjusted mean. A mathematical approximation to this limit is an extremities-trunk ratio less than 1.95 + 1/2 height (m), shown in Fig. 3 as a *dotted line*. For testing the sensitivity of such an auxological screening approach, we collected the data of all children (n = 5; 4 girls) with *SHOX* haploinsufficiency which had been excluded from the mutational screening. The causes of exclusion were obvious Madelung deformity (patient 4), already known nonsense mutation of *SHOX* [patients 5 and 6; both reported by Rao *et al.* (1)] or telomeric deletions of Xp encompassing the *SHOX* locus (patients 7 and 8) (Table 2). All school-age children with *SHOX* haploinsufficiency had an extremities-trunk ratio below the given limit, indicating a high sensitivity (100%) of

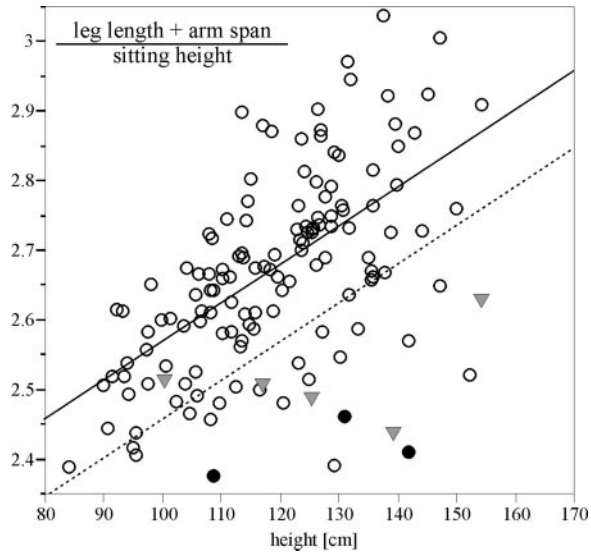

FIG. 3. The extremities-trunk ratio (calculated sum of arm span and subischial leg length, divided by the sitting height) for height can serve as a term that best indicates skeletal disproportion in *SHOX* haploinsufficiency. The *filled circles* mark the three probands with *SHOX* deletion detected in this study. The five *filled triangles* indicate all available patients with SHOX haploinsufficiency who were not included in the screening study. The *solid line* indicates the mean extremities-trunk ratio for height in the total group studied; the *lower dotted line* indicates the mean extremities-trunk ratio minus 1 SD. A mathematical approximation for this *dotted line* was given by the following height-adjusted formula: 1.95 + 1/2 height (m). All patients with SHOX haploinsufficiency except the youngest had ratios below the *dotted line*.

TABLE 2. Characteristics of the five patients with SHOX haploinsufficiency not included in the screening study

	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Controls median
SHOX	Deletion	R195X	R195X	Deletion[a]	Deletion[a]	
Age (yr)	14.6	5.9	8.3	14.4	9.5	9.1
Madelung	yes	no	no	mild	mild	
Height	−3.96	−3.97	−2.70	−1.69	−2.43	−2.99
Sitting height/height	+3.76	+1.62	+2.53	+1.00	+2.26	+0.41
Leg length/sit height	−3.07	−1.33	−2.55	−0.85	−1.99	−0.52
Arm span	−4.53	−2.25	−2.68	−2.75	−3.31	−2.62

Data are given in SD scores for age according to Gerver and De Bruin (16).
[a] 46,X,del(X)(p22.1).

this screening tool for the group of school-age children with SHOX haploinsufficiency (Fig. 3). However, the extent of skeletal disproportion varied. And one child, the youngest and shortest of the group (patient 5), had a low-normal extremities-trunk-ratio for height (2.51 at a height of 100.4 cm) (Fig. 3), which, however, decreased over time to low values for height (2.45 at a height of 125.3 cm). The same increase in skeletal disproportion with time was observed in her older affected brother, patient 6 (2.50 at 117.2 cm, 2.48 at 144.6 cm).

Thus, when testing short school-age children for SHOX haploinsufficiency, the above defined low extremities-trunk ratio less than1.95 + 1/2 height (m) has a sensitivity of 100% and a specificity of 85% for testing SHOX haploinsufficiency according to our data. Assuming a SHOX haploinsufficiency prevalence of approximately 2% in short children, the likelihood that a short school-age child with an extremities-trunk ratio less than 1.95 + 1/2 height (m) has SHOX haploinsufficiency can be estimated to be 12% (positive predictive value of the test). More interestingly, the likelihood that a short school-age child having an extremities-trunk ratio above 1.95 + 1/2 height (m) has no SHOX haploinsufficiency is 100% (negative predictive value) in children with a height above 110 cm. However (as demonstrated by patient 5), in preschool children and in children shorter than 110 cm, this test has a lower sensitivity and specificity and should be used with caution.

Finally, the analysis of the routine left-hand radiographs of the three probands with *SHOX* deletion detected in this study and the radiographs from the other five individuals with previously detected *SHOX* haploinsufficiency were anomalous in showing characteristics of LWD, as shown in Fig. 4 for two of the patients of this screening study: triangularization of the distal radial epiphysis (88%), pyramidalization of the distal carpal row (88%), and lucency of the distal ulnar border of the radius (50%). Because our genetic approach was not able to detect all possible *SHOX* deletions or any *SHOX* point mutation, we also analyzed left-hand x-rays of the 10 individuals with the lowest extremities-trunk ratios in the group of probands with no *SHOX* deletion. Interestingly, one female out of these 10 patients had definitive mild radiological signs of Madelung deformity, which may be caused by an undetected SHOX point mutation or by a mutation of another yet-unknown gene causing LWD. In addition, two other children (3.8 and 5.5 yr) of the 10 patients belonged to the group of five individuals who had only one single fragment size at both SHOX markers but whose paternal DNA was uninformative or missing.

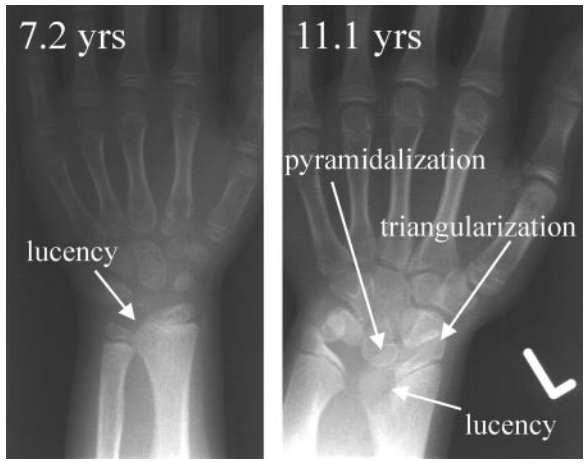

FIG. 4. Radiography of patient 1 (*left*) and patient 2 (*right*) with SHOX haploinsufficiency, showing the main characteristics of mild LWD.

Discussion

The discovery of *SHOX* as an important gene critical to growth promotion has raised the question as to which extent mutations of this gene contribute to short stature previously assigned to be idiopathic. In contrast to a broader definition using idiopathic as a synonym for unexplained, an expert meeting has recently defined idiopathic short stature in detail and excluded children with abnormal body proportions from this definition (15). The rationale of this part of the definition was to not include the wide spectrum of osteochondrodysplasias into the term of idiopathic short stature. However, one has to keep in mind that auxological assessment of short children is often incompletely performed and substituted by the clinical view, which may overlook mild disproportions of the skeleton.

This study is in agreement with previous reports (1, 2, 13) that *SHOX* mutations in children with unexplained short stature are frequent, having an estimated prevalence of at least 1–2%. Taking into account that a certain percentage of individuals with *SHOX* mutations do not have short stature and that the detection of *SHOX* mutations is not complete, a *SHOX* mutation prevalence of at least 1:4,000 in the total population seems to be a good estimate (2). It is therefore very likely that *SHOX* mutations are more frequent than mutations of the fibroblast growth factor receptor (FGFR)3, whose prevalence in achondroplasia has been estimated to be between 1:15,000 and 1:40,000, whereas estimates for hypo-

chondroplasia and some rare osteodysplasias caused by FGFR3 mutations are missing (19).

The estimated high prevalence of *SHOX* haploinsufficiency makes it important to define criteria enabling an early diagnosis in short children, particularly if therapy with recombinant GH proves to be effective in growth promotion (13, 20, 21). Collecting the complete auxological data from all children studied, we observed a definitive disproportionate shortening of arms and legs in all school-age children with *SHOX* haploinsufficiency, in comparison with those with negative screening results. Comparable disproportions of the skeleton attributable to SHOX haploinsufficiency were observed by others whose data were, however, biased by selection because all probands were members of LWD families (11, 22). The skeletal disproportion can be quantified in one term by integrating three commonly used auxological measurements into a ratio. We called it the extremities-trunk ratio, which directly compares extremity lengths (given as calculated subischial leg length plus arm span) with the trunk length (given as sitting height). Our data suggest that the likelihood of the presence of a *SHOX* mutation in short school-age children who have a low height-adjusted extremities-trunk ratio [$<1.95 + 1/2$ height (m)] is approximately 12%. On the other hand, a normal or high-normal extremities-trunk ratio excludes a *SHOX* mutation. This rule is not valid in preschool children with a height less than 110 cm, because skeletal disproportion caused by SHOX haploinsufficiency has not yet sufficiently developed.

Recently, Rappold *et al.* (2) reported mutational screening in short children and detected six functional *SHOX* mutations. Three of the four children with information on the skeletal phenotype had skeletal disproportions. However, no auxological data on body proportions were given. The two siblings from the very first report on the *SHOX* discovery (1), who carried a nonsense mutation, were incorporated as affected controls in this study (patients 5 and 6). They were initially diagnosed with idiopathic short stature when they were 6 and 8 yr old, respectively. Meanwhile, both have developed skeletal disproportions fitting well the diagnosis of LWD. Therefore, clinical diagnosis may be difficult in young children, especially in preschool children when the disproportion of the skeleton has not yet developed. As in LWD families (11), males were underrepresented in the group of so-called idiopathic short children affected with *SHOX* haploinsufficiency (three females and no males in this study; five females and one male in Ref. 2), although males were overrepresented in both screening groups (56% and 60%, respectively). Therefore, the prevalence of females in other studies (5, 11) was not a matter of a screening bias but more likely the result of a fundamental mechanism so-far unknown.

Apart from auxology, a second line of evidence can be drawn from the morphological analysis of the routine left-hand radiography. Although Madelung deformity was clinically apparent only in one control patient affected, we detected mild signs of wrist dysplasia characteristic for LWD in all eight children with *SHOX* haploinsufficiency. The radiographic lucency in the ulnar border of the distal radius is a very early and characteristic sign of wrist dysplasia attributable to LWD, but it was only present in half of our affected children. In contrast, triangularization of the radial epiphysis and pyramidalization of the carpal row (also called carpal wedging) were present in all but one young child with *SHOX* haploinsufficiency. Ross *et al.* (11) found radiological wrist abnormalities compatible with Madelung deformity in only 74% of their 42 probands from LWD families with *SHOX* haploinsufficiency. However, seven of the nine probands found negative for Madelung deformity were below the age of 9 yr; and therefore, ossification of their carpal and radial bones might have been too immature for detailed radiological judgment (23). Schiller *et al.* (5) reported clinical and radiological Madelung deformity in all adults with *SHOX* haploinsufficiency, and emphasized that the first signs of Madelung deformity in childhood, like carpal wedging, are only detectable by radiography. Taken together, the vast majority of patients with *SHOX* haploinsufficiency are likely to develop Madelung deformity. The major drawback of radiological diagnosis in childhood is the missing ossification of the radial epiphysis, which is sufficient at a bone age of 9 yr in girls and 11 yr in boys (23). Therefore, radiological (and clinical) analysis of the supposedly affected parent should be undertaken if the *SHOX* mutation is not *de novo*.

In conclusion, our genetic and clinical analyses indicate that SHOX haploinsufficiency causes a typical pattern of skeletal disproportion and wrist deformation that can be identified by detailed auxological and radiological analysis in the vast majority of affected school-age children. SHOX mutational screening should be restricted to short, school-age children with an extremities-trunk ratio less than $1.95 + 1/2$ height (m). If bone maturation is sufficient and radiological expertise is present, this target group can be further reduced to those children who carry radiological signs of Madelung deformity. The *SHOX* haploinsufficiency phenotypes resemble all grades of LWD and seem to be more frequent than the short stature phenotypes caused by FGFR3 mutations.

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